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Benefit of Intravenous Thrombolysis in Acute Ischemic Stroke Patients with High Cerebral Microbleed Burden

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Abstract

Background and Purpose: Cerebral microbleeds (CMBs) are a risk factor for intracranial hemorrhage. Whether intravenous thrombolysis (IVT) improves functional outcome in acute ischemic stroke patients with CMBs is unknown. We aimed to estimate the treatment effect of IVT in patients with acute ischemic stroke and a high burden (>10) of cerebral microbleeds (CMBs).

Methods: We devised a multi-step algorithm to model 90 days-modified Rankin scale (mRS) scores in patients with ≤ 10 vs. >10 CMBs that do or do not receive IVT. Parameters were extracted from recently published meta-analyses and included pairwise relationships between CMBs, IVT, three-month functional outcome, and intracranial hemorrhage. Uncertainty was quantified in probabilistic sensitivity analyses.

Results: In patients with >10 CMBs as compared to ≤ 10 CMBs, point estimates of the odds ratios for favorable outcome ($mRS \leq 2$) associated with IVT were 7–10% lower, but still greater than 1 (range 1.03–1.51). On the other hand, IVT in patients with >10 CMBs significantly increased the odds of mortality. The point estimates for the net treatment effect of IVT (change in the utility-weighted mRS score) in patients with >10 CMBs were in favor of withholding IVT in older patients with more severe strokes and longer treatment delays. However, as the general pre-test probability of >10 CMBs is low (0.6–2.7%), pre-treatment magnetic-resonance imaging (MRI) to quantify CMB burden would be justified only if it delayed IVT by less than 10 minutes.

Conclusions: High CMB burden modifies the treatment effect of IVT. In patients with >10 CMBs, IVT is associated with higher mortality and – in older patients with severe strokes and longer treatment delays – a net utility loss. Patients with higher-than-average pre-test probability of >10 CMB might profit from MRI-screening if it does not increase the treatment time.

INTRODUCTION

The presence of >10 cerebral microbleeds (CMBs) on magnetic resonance imaging (MRI) is associated with symptomatic intracranial hemorrhage (sICH), poor functional outcome, and mortality in patients with acute ischemic stroke (AIS) treated with intravenous thrombolysis (IVT).¹⁻³ However, to what extent CMBs modify the treatment effect of IVT, and under which circumstances screening for CMBs before IVT might be reasonable, remains unclear.⁴ ⁵ Conducting prospective trials in which patients with many CMBs are randomized to placebo treatment would be logistically challenging and ethically controversial. We aimed to estimate the treatment effect of IVT in AIS patients with high CMB burden using published data concerning the pairwise relationships between CMBs, treatment with IVT, functional outcome (disability and mortality), and the risk of sICH. In addition, we aimed to estimate whether it is justified to perform MRI to screen for CMBs before thrombolysis in all or selected subgroups of patients.

MATERIALS AND METHODS

Data availability

The authors declare that all supporting data are available within the article. Files containing the implementation of the algorithm in MATLAB are available on GitHub (<https://github.com/lshlemm/ThrombolysisCMBs>).

Model

Parameters extracted from the literature describing the relationships between the presence of CMBs, administration of IVT, three-month functional outcome, and the occurrence of sICH are presented in **Table 1**.^{1, 6-10} Whenever possible, we derived parameters from recently published meta-analyses; where such meta-analyses were unavailable, we chose the largest

available prospective cohort studies. A detailed description of the studies from which parameters were extracted is presented in Table I in the Online Supplement. Symptomatic ICH was defined according to the ECASS-2 criteria (clinical deterioration causing an increase in National Institutes of Health Stroke Scale [NIHSS] score of ≥ 4 points, with any hemorrhage on computed tomography [CT]).^{11, 12} High CMB burden was defined as >10 CMBs irrespective of location (deep or lobar) based on previous studies showing an effect on sICH and functional outcome.^{1, 2} The same data suggest no significant effect of 1-10 CMBs vs. no CMBs on disability, mortality, and sICH risk; accordingly, patients without CMBs and patients with 1 to 10 CMBs were grouped together in the current analysis.

The treatment effect of IVT in the group of AIS patients with >10 CMBs and in the group of AIS patients with ≤ 10 CMBs as a function of age, stroke symptom severity (NIHSS score), and treatment delay was estimated using the multi-step algorithm outlined below. In this algorithm, the 7-item distributions of the modified Rankin Scale (mRS) scores were transformed in a step-wise manner using odds ratios pertaining to dichotomized outcomes (good outcome [mRS ≤ 1], favorable outcome [mRS ≤ 2], disability [mRS > 2], and mortality [mRS = 6]) in order to obtain estimates for the three-month functional outcome of AIS patients with and without CMBs that do or do not receive IVT. Within each of the dichotomized mRS groups, the ratios of probabilities were held constant (Figure I in the Online Supplement).

The algorithm consisted of 13 steps (for parameters, see **Table 1**):

1. Modelling the expected distribution of mRS scores at three months for a 71 year old patient not treated with IVT with average risk of CMBs according to NIHSS score. Seventy-one years was the average age in the population used to derive baseline mRS-distributions.⁶
2. Adjustment of the mRS score distribution obtained in (1) for age.
3. Adjustment of mRS score distribution obtained in (2) for treatment with IVT, using the treatment-delay dependent effect of IVT on good outcome and mortality.

4. Estimation of the mRS score distributions for patients treated with IVT according to CMB status (≤ 10 CMBs vs. >10 CMBs), using the mRS score distribution obtained in (3), the effect of >10 CMBs vs. no CMBs in patients treated with IVT on disability and mortality, and the expected proportion of patients with >10 CMBs.
5. Estimation of the mRS score distribution for patients with ≤ 10 CMBs treated with IVT according to the occurrence of sICH (no sICH vs. sICH), using the respective mRS score distribution obtained in (4), the effect of sICH on disability and mortality, and the conditional probability of sICH given treatment with IVT and ≤ 10 CMBs.
6. Repeat (5) for patients with >10 CMBs treated with IVT.
7. Estimation of the effect of >10 CMBs vs. ≤ 10 CMBs in patients treated with IVT on disability and mortality adjusted for the higher risk of sICH, using the mRS score distributions obtained in (5) and (6).
8. Estimation of the mRS score distributions for patients not treated with IVT according to the occurrence of sICH (no sICH vs. sICH), using the mRS score distribution obtained in (2), the effect of sICH on disability and mortality, and the conditional probability of sICH given no treatment with IVT and average probability of CMBs.
9. Estimation of the mRS score distribution for patients with sICH not treated with IVT according to CMB status (≤ 10 CMBs vs. >10 CMBs), using the respective mRS score distribution obtained in (8), the effect of >10 CMBs vs. no CMBs on disability and mortality adjusted for the higher risk of sICH obtained in (7), and the conditional probability of >10 CMBs given no treatment with IVT and occurrence of sICH.
10. Repeat (9) for patients without sICH not treated with IVT.
11. Estimation of the mRS score distribution for patients with ≤ 10 CMBs not treated with IVT, using the respective mRS score distributions from (9) and (10) and the conditional probability of sICH given no treatment with IVT and ≤ 10 CMBs.
12. Repeat (11) for patients with >10 CMBs not treated with IVT.
13. Calculation of the treatment effect of IVT in patients with ≤ 10 CMBs, using the respective mRS score distribution obtained in (4) and the mRS score distribution obtained in (11). Calculation of the treatment effect of IVT in patients with >10 CMBs, using the respective mRS score distributions obtained in (4) and the mRS score distribution obtained in (12).

A visualization of the algorithm is presented in **Figure 1**. The primary outcome measure of our analysis was the treatment effect of IVT in patients with >10 CMBs and patients with ≤ 10 CMBs, quantified as the (a) odds ratio for good functional outcome ($mRS \leq 2$), (b) the odds ratio for mortality, and (c) the change in the utility-weighted mRS score at three months associated with IVT. Utility weights were chosen as the arithmetic mean from two recently published studies.^{13, 14}

Only MRI allows quantification of CMBs. However, MRI acquisition will incur additional delays to treatment.¹⁵ We therefore estimated the maximum justifiable time to obtain MRI for the quantification of CMB burden that would be associated with a net clinical benefit of IVT. The maximum justifiable time to obtain MRI was calculated using the net effect of IVT in patients with >10 CMBs and the time-decay slope of the point estimate curve of the net benefit of IVT in patients with ≤ 10 CMBs. All analyses were performed with MATLAB.¹⁶

Sensitivity analyses

The effect of uncertainty surrounding the input parameters was quantified in probabilistic sensitivity analyses (PSA). For this, calculations were repeated 10,000 times with parameters drawn independently from their respective probability distributions. Parameters were considered normally distributed except for probabilities, for which beta-distributions were used. Results of PSA are presented as 95% equal-tailed credible intervals in which the estimated outcome measure falls with 95% probability. Data describing the relative effect of >10 CMBs vs. no CMBs on the risk of sICH were only available for patients treated with IVT. In the base case model, we assumed the same relative effect of >10 CMBs on the risk of sICH for patients not treated with IVT. To assess the impact of this assumption, we also performed all calculations assuming that CMBs had no impact on the risk of sICH in untreated patients. Furthermore, in the base case model, we assumed no association between

age and treatment effect size of IVT. However, since CMB burden increases with age¹⁰, an association between the presence >10 CMBs and the treatment effect of IVT would be expected to lead to slightly lower treatment effect sizes in older patients; such a correlation between increasing age and lower treatment effect size was observed in a recent meta-analysis albeit without reaching statistical significance.⁸ To investigate the impact of this uncertainty on the results of our model, we performed an additional sensitivity analysis including age as an additional modifier of the treatment effect size of IVT.

Standard Protocol Approvals, Registrations, and Patient Consents

No informed consent and no ethical approval was required for this study.

RESULTS

The available published information on the relationship between IVT, presence of CMBs, functional outcome, and the occurrence of sICH (**Table 1**) were sufficient to derive estimates of the treatment effect of IVT in the subgroup of AIS patients with ≤ 10 CMBs and with > 10 CMBs using a multi-step algorithm.

Favorable outcome (mRS ≤ 2)

The point estimates for a beneficial treatment effect of IVT on functional outcome (odds ratio for favorable outcome [mRS ≤ 2]) were consistently lower among patients with > 10 CMBs as compared to patients with ≤ 10 CMBs (relative difference of the treatment effect sizes (odds ratios) ranging from -10% to -7% depending on age, stroke symptom severity, and treatment delay). The 95% credible intervals of the treatment effects of IVT with regards to favorable outcome in patients with ≤ 10 CMBs and patients with > 10 CMBs overlapped. In absolute terms, the point estimates for a beneficial treatment effect of IVT on functional outcome among patients with > 10 CMBs were consistently positive (odds ratio > 1 , range 1.03 – 1.51)

across the entire treatment time window (30 – 270 min). However, depending on age and stroke symptom severity, the lower bound of the 95% credible interval crossed the line of no effect (odds ratio of 1) at a treatment delay between 120 and 210 min. (**Figure 2, top row**).

Mortality

The point estimates for the treatment effect of IVT on mortality were higher among patients with >10 CMBs as compared to patients with ≤ 10 CMBs (relative difference of the treatment effect sizes (odds ratios) ranging from 7% to 25%, depending on age and stroke symptom severity, irrespective of treatment delay). The 95% credible intervals of the treatment effect of IVT with regards to mortality in patients with ≤ 10 CMBs and patients with >10 CMBs overlapped. In absolute terms, depending on age and stroke symptom severity, the point estimates of the treatment effect of IVT on mortality among patients with >10 CMBs ranged from 1.16 – 1.38; the lower bound of the 95% credible interval did not cross the line of no effect (odds ratio of 1). (**Figure 2, middle row**)

Utility-weighted mRS score

To analyze the combined treatment effects of IVT on disability and mortality, utility-weighted mRS scores were calculated. Among patients with ≤ 10 CMBs, IVT was associated with a net benefit, irrespective of age, stroke symptom severity, and treatment delay. Compared to patients with ≤ 10 CMBs, the net benefit of IVT among patients with >10 CMBs was consistently lower; this difference reached statistical significance (i.e. with no crossing of the 95% credible intervals) for older patients with more severe stroke symptoms (age: 80 years, NIHSS score: 15; **Figure 2, bottom row**).

Among patients with >10 CMBs, the point estimates of the net benefit of IVT could be either positive or negative; the probability of net harm caused by IVT was correlated with increasing age, stroke symptom severity, and treatment delay. For example, for a 60- year old

patient with an NIHSS score of 5, the point estimate of net benefit of IVT was positive up to treatment delay of 262 min; for an 80-year old patient with an NIHSS score of 15, on the other hand, there was no net clinical benefit across the entire treat time window (**Figure 3**). The 95% credible intervals contained the line of no effect (absolute net benefit of 0) across the entire treatment time window (30 – 270 min; **Figure 2, bottom row**).

Maximum justifiable time to obtain MRI

In summary, the net benefit of IVT among patients with <10 CMBs was positive, but decreased as treatment delay increased, whereas, in certain circumstances, IVT in patients with >10 CMBs was associated with a risk of net harm. Given an age-specific pre-test probability of >10 CMBs between 0.6% and 2.7% in the general population^{1, 10}, the maximum justifiable time to obtain MRI before IVT associated with a net benefit was short: depending on age and NIHSS score, the point estimates ranged from 0 to 10 min. The upper limits of the 95% credible interval reached a maximum of 24 min for 90 year-old patients with severe strokes (NIHSS score 20). For patients aged ≤ 80 years, the upper limit of the 95% credible interval was below 11 min (**Figure 4**). For individuals with a higher pre-test probability of >10 CMBs, the justifiable time to obtain MRI for pre-treatment quantification of CMB burden would be longer; more specifically, the maximum justifiable time to obtain MRI and the pre-test probability of >10 CMBs exhibit a directly proportional relationship such that if the pre-test probability of >10 CMBs increases by a factor f , so does the justifiable time to obtain MRI before IVT.

Univariate sensitivity analyses

Repeating the analyses under the assumption that there was no effect of >10 CMBs vs. no CMBs on the risk of sICH in patients not treated with IVT resulted in a slightly smaller estimated treatment effect of IVT in patients with >10 CMBs and slightly longer maximum

justifiable times to obtain MRI, but did not affect the interpretation of our study. Running a modified model that included age as a treatment effect modifier of IVT also yielded results very similar to those obtained in the base case model (**Figure 5**).

DISCUSSION

Main findings

We used a multi-step algorithm populated with data from clinical studies to estimate three-month functional outcome in AIS patients with high CMB burden (>10 CMBs). Our main findings are 1) that the beneficial treatment effect of IVT on favorable outcome is attenuated in patients with >10 CMBs as compared to patients with ≤ 10 CMBs; 2) that IVT is associated with a statistically significantly increased risk of mortality in patients with >10 CMBs; and 3) that treatment with IVT might be associated with net harm in subgroups of patients with >10 CMBs defined by age, stroke symptom severity, and treatment delay; nevertheless, 4) routine pre-treatment MRI to quantify CMB burden before IVT cannot generally be recommended, as long as it causes even a small additional treatment delay.

Clinical implications

Our results might have important implications for clinical practice and future research directions. According to current American Heart Association/American Stroke Association guidelines, available data does not allow determination of the effect of baseline CMBs on the treatment effect of IVT; in patients with >10 CMBs, the benefits of treatment with IVT are uncertain.⁵ As a consequence, the guidelines do not recommend routine use of MRI to exclude CMBs before administration of IVT. Our study is the first to quantitatively estimate the extent to which high burden of CMBs might affect the treatment effect of IVT, and to provide upper limits for the maximum additional delay to IVT that pre-treatment MRI should

incur in order not to cause harm. Our results indicate that in older patients with more severe strokes and a previously demonstrated high burden of CMB on MRI, treatment with IVT might be harmful. Our findings support the current practice of not routinely obtaining pre-treatment MRI to screen for CMBs prior to IVT. However, contrary to current practice, our findings suggest that in some patients with a high likelihood of >10 CMBs, e.g. due to advanced age (>80 years) in combination with a known history of dementia, evidence of cerebral small vessel disease on a prior CT scan, or a previous history of spontaneous intracerebral hemorrhage, performing pre-treatment MRI and withholding IVT in case of >10 CMBs might be associated with net clinical benefit even if the additional delay to treatment caused by MRI is considerably longer. This would apply in particular to patients with moderate to severe stroke symptoms who present late in the treatment time window. Prospective studies or trials investigating the benefit of pre-treatment MRI in this patient population, which is expected to grow, are warranted.

Limitations

We are aware of possible limitations of our study. The parameters used in our algorithm to estimate functional outcomes in specific patients groups were derived from studies that included patients who were not treated with mechanical thrombectomy and who were predominantly Caucasian. As the bleeding risk in Asian populations is higher compared to European and North American populations, our results cannot be generalized to patients with Asian background. Similarly, our results do not apply to patients who receive IVT as bridging therapy to mechanical thrombectomy. In addition, parameters describing the association between CMBs and outcome were extracted from studies that required participants to be able to undergo MRI, which could have introduced bias. Similarly, a subset of parameters was derived from studies that only included patients without pre-stroke disability. Furthermore, due to lack of data, we had to assume that the relative effect of sICH on functional outcome

observed in patients treated with IVT with an average number of CMBs can be generalized to patients not treated with IVT and to patients with different number of CMBs. However, it seems plausible from a pathophysiological point of view that the occurrence of sICH has a similar relative effect in all of these patient populations. Last, no studies reporting directly on the risk of sICH in patients without IVT stratified by CMB status could be identified. In the base case analysis, we therefore assumed that the relative effect of >10 CMBs vs. no CMBs observed in patients treated with IVT can also be applied to patients not treated with IVT. However, this parameter was not critical to the overall interpretation of our study as sensitivity analysis yielded similar results when the former assumption was modified (i.e., no effect of >10 CMBs on the risk of sICH in patients not treated with IVT). Due to these limitations, confirmation of our findings is necessary. We chose a cutoff of >10 CMBs because smaller numbers have not been found consistently to be associated with outcome and risk of sICH.¹

Conclusions

Our modelling suggests that high CMB burden is a treatment effect modifier of IVT. In patients with >10 CMBs, IVT is associated with higher mortality and – in older patients with severe strokes and longer treatment delays – a net utility loss. Examples of clinical characteristics of patients with >10 CMBs in which IVT is expected to cause net harm include: age ≥ 80 years with NIHSS score ≥ 15 irrespective of treatment delay; age ≥ 80 years with NIHSS score ≥ 5 and treatment delay ≥ 4.0 hours; or age ≥ 60 years with NIHSS score ≥ 15 and treatment delay ≥ 2 hours. However, based on our analysis, screening with MRI is not justified unless it can be performed nearly as quickly as CT or unless additional clinical information indicate a higher-than-average pre-test probability of CMBs.

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Figure Legends

Figure 1. Schematic diagram of the algorithm

Three-month functional outcome was estimated for different groups of ischemic stroke patients defined by CMB-status (>10 vs. ≤ 10 vs. average number), occurrence of sICH (yes vs. no vs. at risk) and treatment status (IVT vs. no IVT). Resulting mRS-distributions were used to estimate the treatment effect of IVT in groups of patients with >10 and ≤ 10 CMBs. Circled numbers correspond to steps of the algorithm described in the Methods section.

IVT stands for intravenous thrombolysis; mRS, modified Ranking scale; CMB, cerebral microbleeds; sICH, symptomatic intracranial hemorrhage; NIHSS, National Institutes of Health Stroke Scale.

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Figure 2. Treatment effect of intravenous thrombolysis in acute ischemic stroke patients with ≤ 10 vs. > 10 cerebral microbleeds

The shaded areas visualize 95% credible interval derived from probabilistic sensitivity analyses. **Top row:** Odds ratio (OR) for a good functional outcome, defined as a modified Rankin scale (mRS) score ≤ 2 at 90 days. **Middle row:** OR for mortality at 90 days. **Bottom row:** Absolute difference of net clinical benefit at 90 days. The net clinical benefit is calculated as the change of the utility-weighted mRS score associated with intravenous thrombolysis (IVT). Horizontal bars at the bottom of the panels visualize treatment delays at which IVT is estimated to cause net benefit (green/light) and net harm (red/dark) for patients with > 10 CMBs. NIHSS stands for National Institutes of Health Stroke Scale score; CMBs, cerebral microbleeds.

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Figure 3. Treatment delay thresholds for intravenous thrombolysis-associated net harm among patients with >10 cerebral microbleeds

Shown are minimum treatment delays (from symptom onset) above which the point estimates for the net benefit of intravenous thrombolysis in acute ischemic stroke patients with >10 cerebral microbleeds and different combinations of age and National Institutes of Health Stroke Scale (NIHSS) score are negative (net harm).

Figure 4. Maximum justifiable additional time to obtain magnetic resonance imaging

Shown are estimates for the maximum additional time to perform magnetic resonance imaging (MRI) before the initiation of intravenous thrombolysis (IVT) to identify patients with >10 cerebral microbleeds (CMBs) associated with a net clinical benefit as compared to not performing MRI. Crosses ('x') denote combinations of clinical characteristics for which point estimates of the net benefit of IVT in patients with >10 CMBs are positive, and thus the maximum justifiable additional time to obtain MRI is zero. CI stands for credible interval; NIHSS, National Institutes of Health Stroke Scale score

Figure 5. Results of univariate sensitivity analyses

Shown are estimates for the maximum additional time to perform magnetic resonance imaging (MRI) before the initiation of intravenous thrombolysis (IVT) to identify patients with >10 cerebral microbleeds (CMBs) associated with a net clinical benefit as compared to not performing MRI that were obtained when base case assumptions of the model were varied in sensitivity analyses:

- **S₁^o (base case)**: Same relative effect of >10 CMBs on the risk of symptomatic intracranial hemorrhage (sICH) for patients not treated with IVT as for patients treated with IVT vs. **S₁⁺**: No effect of >10 CMBs on the risk of sICH in patients not treated with IVT.
- **S₂^o (base case)**: No association between age and treatment effect size of IVT vs. **S₂⁺**: Lower treatment effect size of IVT in older patients.

Groups of bars correspond to different combinations of clinical characteristics (age [years], stroke symptom severity [National Institutes of Health Stroke Scale score] and treatment delay [minutes]) outlined in the table below the chart. Symbols denote point estimates, shaded bars extend to the upper bound of 95% credible intervals.

Tables

Table 1 Parameters extracted from published studies			
Parameter	Measure	Value, point estimate (95% CI)	Reference
Distribution of mRS categories at 90 days without treatment, according to NIHSS score	%	Supplemental Figure 1	Whitely et al. ⁶
Effect of age on ...			
... favorable outcome, mRS ≤ 2	Odds ratio	46 – 55 years: 1.5 (1.2 – 1.9) 56 – 65 years: 1 (Reference) 66 – 75 years: 0.7 (0.6 – 0.81) 76 – 85 years: 0.32 (0.28 – 0.37) 85 – 95 years: 0.18 (0.14 – 0.22)	Knoflach et al. ⁷
Effect of IVT in patients with average number of CMBs on ...			
... good outcome, mRS ≤ 1	Odds ratio	30 min: 1.99 (1.36 – 2.87) 270 min: 1.24 (1.09 – 1.40)	Emberson et al. ⁸
... mortality	Odds ratio	1.11 (0.99 – 1.25)	
... risk of sICH	Odds ratio	5.55 (4.01 – 7.7)	
Effect of age on ...			
... beneficial treatment effect of IVT with regards to good outcome, mRS ≤ 1	Proportionality factor	50 years: 1.06 60 years: 1.03 71 years: 1.00 (Reference) 80 years: 0.97 90 years: 0.95	Emberson et al. ⁸ , only considered in sensitivity analysis
Effect of >10 CMBs vs. no CMBs in patients treated with IVT on ...			
... disability, mRS >2	Odds ratio	3.99 (1.55 – 10.22)	Charidimou et al. ¹
... mortality	Odds ratio	2.44 (1.00 – 6.49) ‡	
... risk of sICH *	Odds ratio	3.65 (1.17 – 11.42)	
Effect of sICH in patients treated with IVT with average number of CMBs on ...			
... disability, mRS >2 †	Odds ratio	2.68 (2.35 – 3.19)	Strbian et al. ⁹
... mortality †	Odds ratio	5.19 (3.55 – 7.65)	
Expected proportion of patients with >10 CMBs according to age:	%	50 - 59 years: 0.60 (0.50 - 0.71) 60 - 69 years: 0.88 (0.74 - 1.03) 70 - 79 years: 1.95 (1.57 - 2.35) >80 years: 2.68 (1.99 - 3.43)	Charidimou et al. ¹ Poels et al. ¹⁰
Frequency of sICH in patients with average number of CMBs ...			
... with IVT	%	7.0 (5.6 – 8.8)	Strbian et al. ⁹
* In the base case scenario, same odds ratio assumed for patients not treated with IVT; the impact of this assumption was explored in univariate sensitivity analyses. † Same odds ratios assumed for patients treated with IVT with ≤ 10 or >10 CMBs, and for patients not treated with IVT with average number of CMBs. ‡ An odds ratio < 1 was considered implausible. mRS stands for modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; CI, confidence interval; IVT, intravenous thrombolysis; CMBs, cerebral microbleeds; sICH, symptomatic intracranial hemorrhage (according to ECASS-2 definition).			

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① ②

Estimate 90-day mRS **without** IVT as a function of NIHSS score and age

mRS
CMBs: average
sICH: at risk
no IVT

③

Estimate 90-day mRS **with** IVT as a function of NIHSS score, age, and treatment delay

mRS
CMBs: average
sICH: at risk
IVT

IVT

④

mRS
CMBs: ≤10
sICH: at risk
IVT

④

mRS
CMBs: >10
sICH: at risk
IVT

⑤

mRS
CMBs: ≤10
sICH: yes
IVT

⑤

mRS
CMBs: ≤10
sICH: no
IVT

⑥

mRS
CMBs: >10
sICH: yes
IVT

⑥

mRS
CMBs: >10
sICH: no
IVT

⑦

Effect of >10 CMBs vs. ≤10 CMBs in patients treated with IVT, adjusted for the higher risk of sICH

No IVT

⑧

mRS
CMBs: average
sICH: yes
no IVT

⑧

mRS
CMBs: average
sICH: no
no IVT

⑨

mRS
CMBs: ≤10
sICH: yes
no IVT

⑨

mRS
CMBs: >10
sICH: yes
no IVT

⑩

mRS
CMBs: ≤10
sICH: no
no IVT

⑩

mRS
CMBs: >10
sICH: no
no IVT

⑪

mRS
CMBs: ≤10
sICH: at risk
no IVT

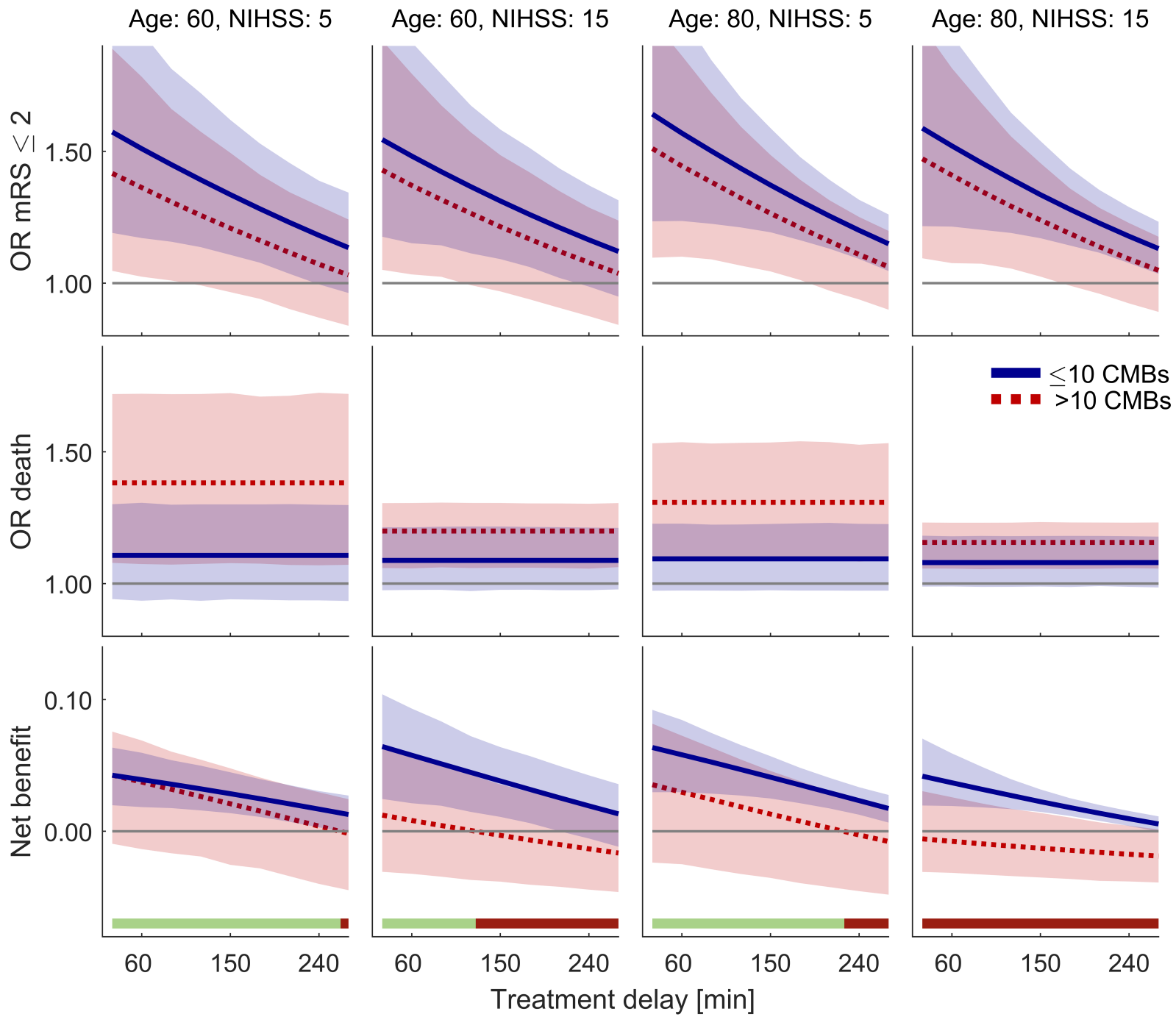
⑫

mRS
CMBs: >10
sICH: at risk
no IVT

Treatment effect of IVT in patients with ≤10 CMBs

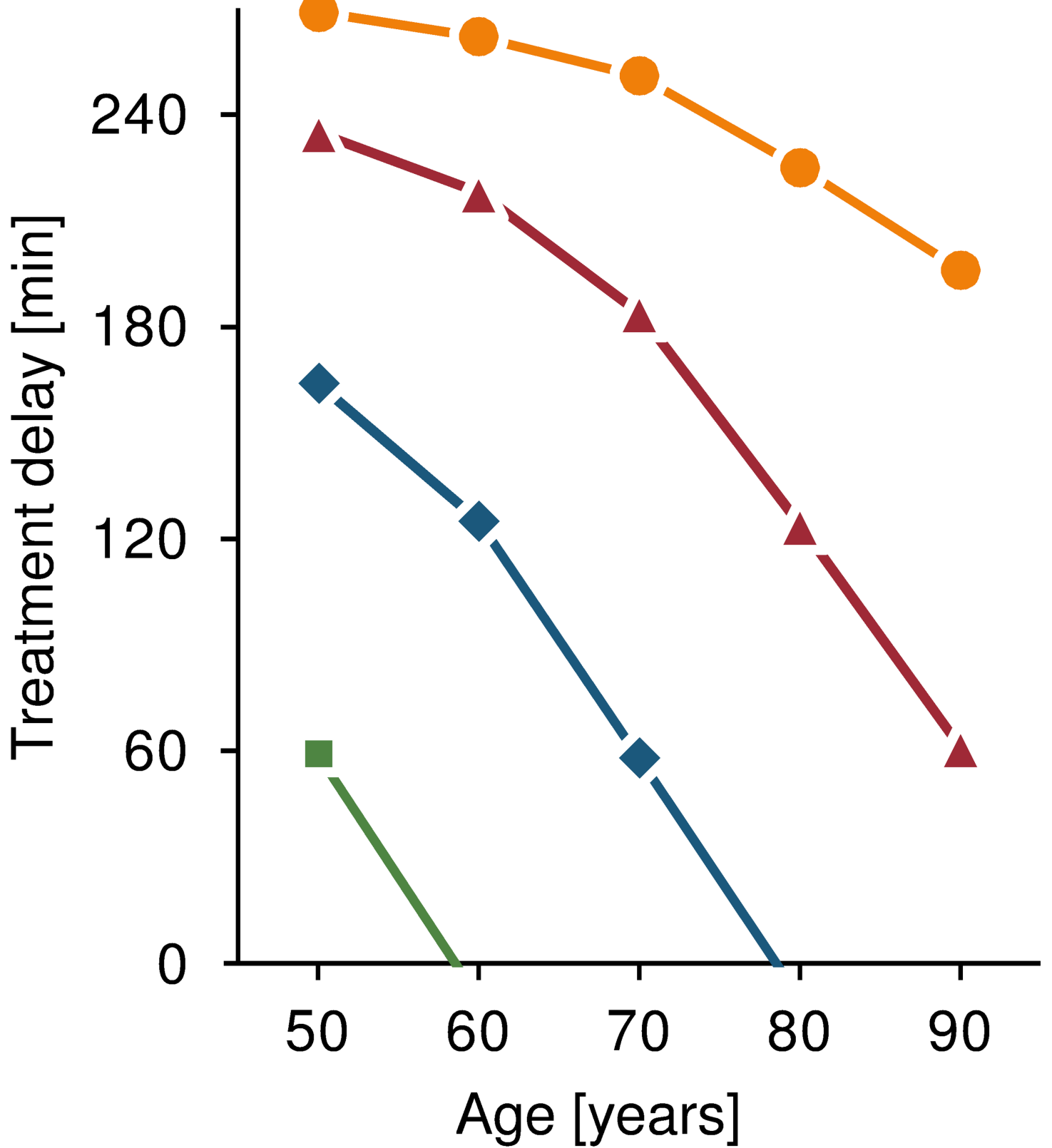
⑬

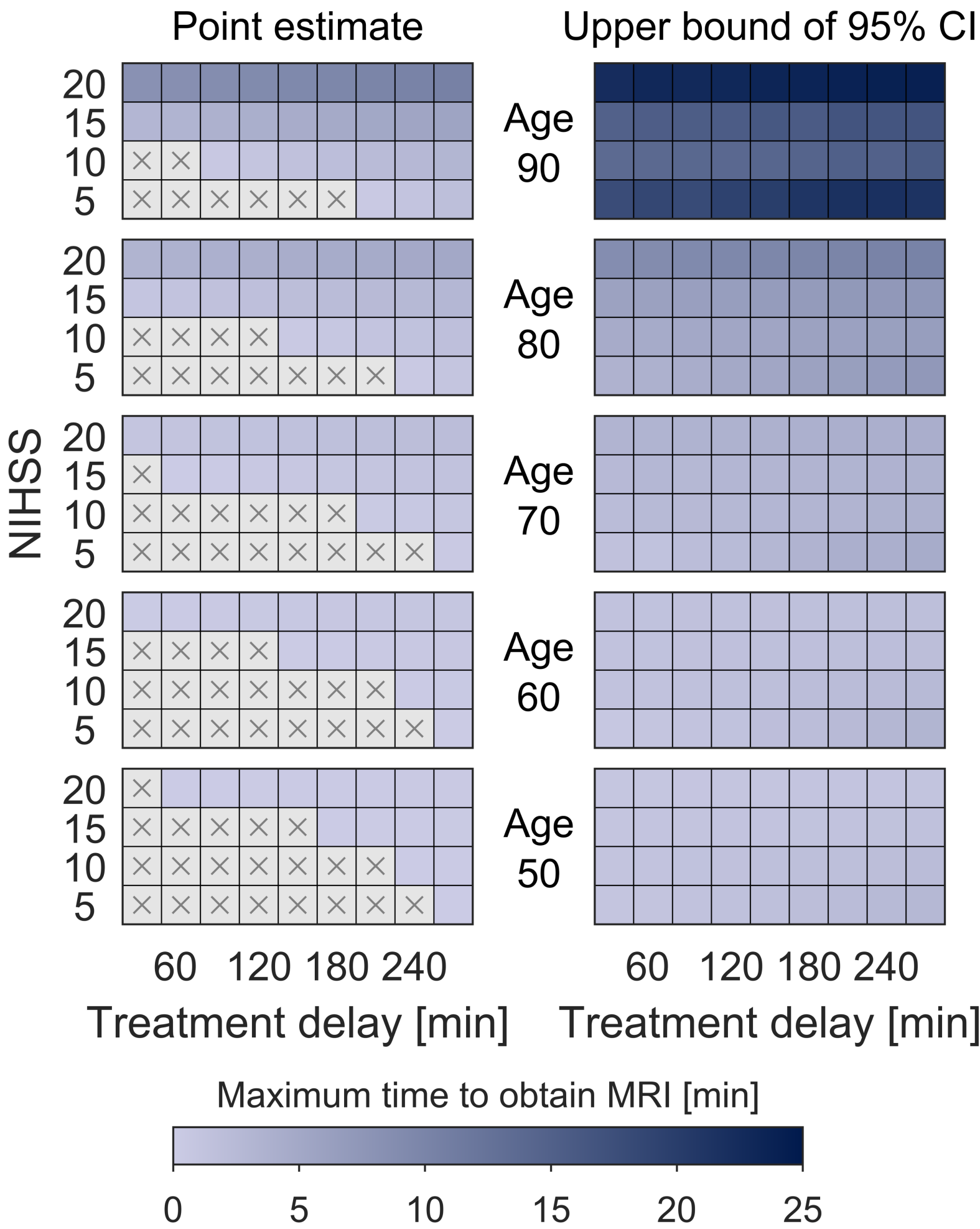
Treatment effect of IVT in patients with >10 CMBs

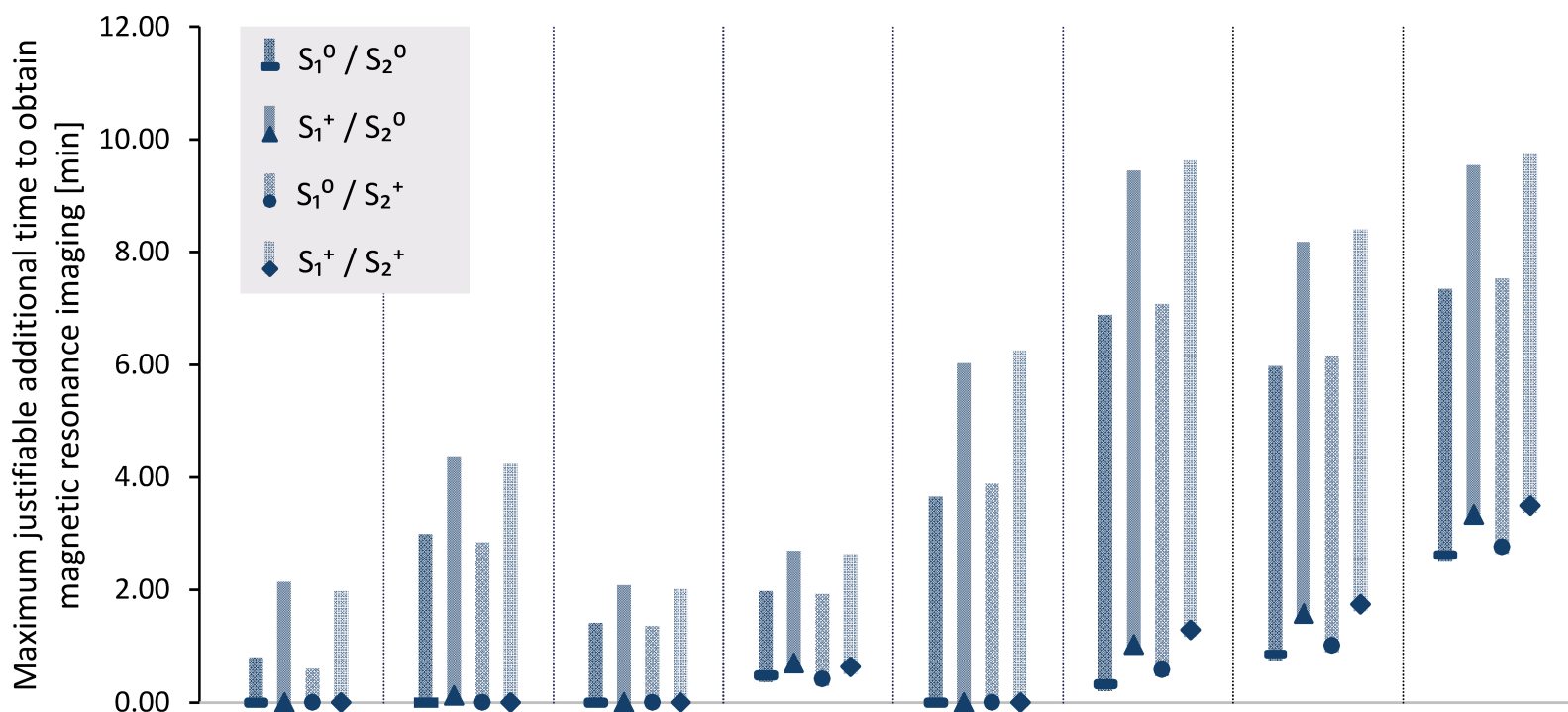


NIHSS score

—●— 5 —▲— 10 —◆— 15 —■— 20







Patient characteristics

Age	60	60	60	60	80	80	80	80
NIHSS	5	5	15	15	5	5	15	15
Delay	30	240	30	240	30	240	30	240